Longwave Ultraviolet Radiation (UVA, 320–400 nm)-Induced Tan Protects Human Skin Against Further UVA Injury

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The protective effect of a UVA (320–400 nm) induced tan against cutaneous injury by further UVA-irradiation was studied by evaluating the histopathologic changes in tanned and untanned normal human buttock skin 24 h after exposure to 2 and 4 minimal erythema doses of UVA.

In each subject there were fewer polymorphonuclear leukocytes and less endothelial cell prominence and vessel wall necrosis in the UVA tanned skin than in the untanned UVA-irradiated skin. In the tanned control and tanned UVA-irradiated skin there was a prominent mononuclear cell inflammatory infiltrate that was much greater than in untanned skin. In immunoperoxidase stained tissue sections, the mononuclear cells were predominantly T cells, and in all of the specimens the number of phenotypic helper/inducer cells exceeded the phenotypic cytotoxic/suppressor cells.

This demonstrates that a UVA tan provides photoprotection against acute UVA exposure. In addition, tanning, with or without further UVA-irradiation, was associated with a mononuclear cell inflammatory infiltrate. *J Invest Dermatol 93:713–718, 1989*

Human exposure to UVA (320–400 nm) radiation is increasing because of growing use of UVA "sun" tanning parlors, and the increased effectiveness of UVB (280–320 nm) sunscreens, which allow for more prolonged sun exposure and increased selective exposure to UVA.

Although UVA is about 1000 times less erythemogenic than UVB, there is about 100 times more UVA than UVB in sunlight, and there is evidence to suggest that chronic UVA exposure not only contributes to the carcinogenic effects of sunlight but also has a role in aging of the skin [1–4].

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Abbreviations:
CD: cluster of differentiation
H&E: hematoxylin and eosin
IL-1: interleukin-1
MED: minimal erythema dose
MNC: mononuclear inflammatory cells
PBS: phosphate-buffered saline
PMN: polymorphonuclear leukocytes
TNF: tumor necrosis factor
UVA: long ultraviolet
UVB: middle ultraviolet
UVC: short ultraviolet

UVA predominantly affects the dermis, while UVC (200–280 nm) and UVB primarily affect the epidermis when, given in equally erythemogenic doses [5]. Miescher first observed that suberythemogenic doses of UVA to the skin caused endothelial cell necrosis with minimal injury to the epidermis [6]. Since then other investigators have observed endothelial cell damage in UVA- but not UVC- or UVB-irradiated specimens [5,7–9].

Although UVA effectively induces a tan, the resulting pigment is poorly protective against UVB induced erythema when compared to a visually similar UVB-induced tan [10]. This finding may be accounted for by the fact that there is no epidermal thickening in a UVA tan, and the increased melanin is predominantly in the basal layer, whereas in a UVB tan the epidermis is thickened and the pigment is distributed throughout the epidermis and stratum corneum, thereby affording better optical protection [11].

We have undertaken this study to determine if a UVA tan protects against acute dermal injury induced by further UVA-radiation using vascular damage and inflammation as our end-points.

MATERIALS AND METHODS

Subjects Seven healthy Caucasians (six male and one female, 26 to 46 years of age) were enrolled in the study after giving informed consent. Three volunteers had skin type I or II and four had skin type III or IV [12]. None of the volunteers was on any medication, and none had a history of an abnormal reaction to sun exposure. The initial UVA tanning and the subsequent acute UVA irradiation were performed on normal buttock skin.

UVA Source A high intensity UVA-radiation source (UVASUN 2000, Mutzhas Co., Munich, West Germany) that emits predominately between 340–450 nm was used. An Optronics 742 spectroradiometer (Optronic Laboratories, Inc., Orlando, FL) showed that visible light (400–800 nm) made up approximately 25% of the total radiant energy, and no radiation below 340 nm was detected. The

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UVA-irradiance averaged 36 mW/cm² over a 12 × 10 cm square field, with a uniformity of ± 10%.

Radiometry was performed before each exposure using an International Light (International Light, Newburyport, MA) broadband UVA detector with a peak sensitivity at 360 nm and an International Light 1700 radiometer.

Experimental Protocol The minimal erythema dose (MED) of UVA-radiation was determined by exposing buttock skin to increasing doses of UVA radiation, beginning at 20 J/cm², with 10 J/cm² increments. Erythema was assessed 24 h later, and the lowest dose of irradiation that resulted in erythema filling the exposure site was considered to be the MED. The MED of the seven volunteers varied between 30–50 J/cm², depending on their skin type. The UVA tan was induced on three 2 × 3 cm sites on the buttock of each volunteer by exposure to 1 MED of UVA-radiation on days 1, 3, 5, and 8. In each subject with type III or IV skin, the tanning exposures resulted in moderate uniform pigmentation with well-defined margins. In skin type I or II subjects, the tan was not as dark, but was uniform and had well-defined margins. One week after the last tanning exposure, 1 × 1 cm sites on tanned and untanned skin were exposed to 2 and 4 MED of UVA.

Tissue Preparation Twenty-four hours after acute UVA exposure, six 4-mm trephine biopsies were obtained from each of the seven patients, using 2% xylocaine without epinephrine for intradermal anesthesia. Four specimens were from tanned and untanned sites acutely exposed to 2 and 4 MED of UVA. The other two specimens came from tanned and untanned control skin. Each biopsy specimen was bisected. One-half of the specimen was fixed in 10% buffered formalin. It was then routinely processed, and the hematoxylin and eosin (H&E) stained tissue sections were examined by light microscopy. The other half of the tissue specimen was immediately frozen in OCT compound (Ames Co., Division of Miles Laboratories, Inc., Elkhart, IN), and stored at −70°C. Four-micrometer cryostat tissue sections were air-dried, fixed in acetone for 10 min, then rinsed with phosphate-buffered saline (PBS). Tissue sections were then stained with monoclonal antibodies using a three-step avidin-biotin immunoperoxidase technique [13]. The sections were preincubated in normal horse serum for 20 min and then incubated for 1 h with optimal concentrations of the murine-derived monoclonal antibodies listed below. This was followed by incubation with biotinylated horse anti-mouse immunoglobulin for 30 min and an avidin-biotinylated peroxidase complex (Vector Laboratories, Inc., Burlingame, CA) for 45 min. Sections were then stained by incubation with 3-amino-9-ethylcarbazole (Aldrich Chemical Co., Milwaukee, WI) and hydrogen peroxide until a visible reaction product developed. They were then counter-stained with Gill's triple strength hematoxylin and examined by light microscopy [14].

The primary antibodies used were OKT6, OKM1, OKT8 (Ortho Diagnostic Systems, Raritan, NJ), anti-HLA-DR, Leu-3a, Leu 4, and Leu 10 (Becton-Dickinson Monoclonal Center, Inc., Mountain View, CA) (Table I) [15].

Evaluation of Specimens and Analysis of Data Both the H&E and immunoperoxidase stained tissue sections were viewed in a coded manner. Each H&E stained tissue section was evaluated for epidermal thickness, dyskeratotic "sunburn" cells, maturation disarray, melanocyte shape and prominence of dendrites, and pigmentation of keratinocytes. The dermal inflammatory cell infiltrate in all of the tissue specimens was quantified using an ocular grid at 40× magnification, and counting the number of polymorphonuclear leukocytes (PMN) and mononuclear inflammatory cells (MNC) in four 0.0313 mm² fields in both the upper and lower dermis. Cell numbers were expressed as cells per mm² [16]. In the immunoperoxidase stained tissue sections, the number of epidermal Langerhans cells, as stained by CD1a and anti-HLA-DR antibodies, were counted per linear mm of epidermis. The dermal MNC infiltrate was evaluated in a semiquantitative manner by comparing immunoperoxidase stained to unstained cells. The stained cells were graded on a scale of 1–4+. (1+ = 0–25%, 2+ = 26–50%, 3+ = 51–75%, 4+ = 76–100% stained cells). The immunoperoxidase studies were done on six of seven subjects; one of the anti-HLA-DR stained specimens was inadequate. The effects of a UVA tan and the dose of acute UVA irradiation on quantitative cell counts were assessed by three-way mixed effects analysis of variance. This statistical technique evaluates the effect of the independent variable of interest (i.e., UVA tan or dose of acute UVA-irradiation) after adjusting for the effect of the other independent variable and the variation among subjects. Paired t-tests were used for the comparisons between tanned and untanned control specimens. Unpaired t-tests were used for univariate comparisons between subjects of different skin types [17].

Table I. Monoclonal Antibodies

Monoclonal antibody	Class	Cluster of differentiation	Reactivity with mononuclear cells
Anti-Leu-4	IgG1	CD3	Pan T cells
Anti-Leu-3a	IgG1	CD4	Helper/inducer T cells (T cells reactive with class II MHC antigens) monocytes/ macrophages
Anti-T8 (OKT8)	IgG2a	CD8	Cytotoxic/suppressor T cells
Anti-T6 (OKT6)	IgG1	CD1a	Langerhans cells (cortical thymocytes)
Anti-M1 (OKM1)	IgG2b	CD11	Monocytes, NK cells, granulocytes
Anti-HLA-DR (BDIa)	IgG2a	—	Pan B cells (not in tissue plasma cells), activated T cells, Langerhans cells and interdigitating reticulum cells, monocytes/ macrophages, endothelial cells; certain epithelial cells
Anti-HLA-DQ (Leu10)	IgG1	—	B cells, monocytes/ macrophages, T cell blasts, dendritic cells

RESULTS

In the untanned control skin, the epidermis was 4–10 cell layers thick, and melanin granules were seen in the cytoplasm of some of the keratinocytes in the lower half of the epidermis. The melanocytes had small round or crescent shaped nuclei, with very scant cytoplasm and no visible pigment.

In the tanned control specimens, the epidermis was 4–12 cell layers thick with scant intra- and intercellular edema, and there was more keratinocytic pigmentation in the lower half of the epidermis than seen in untanned controls. The melanocytes were enlarged. They had round to oval pale nuclei with uniformly dispersed chromatin and increased cytoplasm with elongated dendrites which contained some fine melanin pigment. In the dermis there was scant perivascular edema and vasodilatation, with some thickening of the vessel walls in the superficial dermis. A perivascular MNC infiltrate was present in the upper and mid dermis.

In the acutely irradiated untanned skin, the most striking findings were in the dermis. There was infarctive necrosis and loss of endothelial cells in some of the superficial capillary venules and vessels in the superficial venular plexus. Other vascular changes included vasodilatation and endothelial cell prominence extending into the mid dermis. There was a prominent infiltrate of PMN, along with some MNC in the upper and mid dermis. These changes were most prominent after exposure to 4 MED of UVA-radiation. The epi-

dermis was 4–11 cell layers thick, and there was intra- and intercellular edema with a loss of normal maturation from the basal to the granular cell layer. There was no evidence of dyskeratotic "sunburn" cells, and the pigmentation of keratinocytes was similar to that seen in untanned control specimens. The melanocytes had more uniformly oval to round nuclei with more cytoplasm than in normal controls. Although this was similar to that seen in tanned controls, the nuclear chromatin was more hyperchromatic in the untanned UVA-irradiated specimens (Fig 1). There was also an occasional binucleated melanocyte.

Acute UVA irradiation in previously tanned skin resulted in less severe alterations. In the dermis there was a prominent MNC infiltrate in the upper and mid dermis. PMN were present, but were less numerous than in untanned UVA-irradiated sites. In addition to vessel wall thickening, similar to that seen in tanned control specimens, there was some vasodilatation and endothelial cell prominence, without any vessel wall or endothelial cell necrosis. The epidermis was similar to that seen in tanned controls, although there was more intra- and intercellular edema, basal layer vacuolization, and vertical elongation of keratinocytes. While melanocyte size, shape, and pigmentation were similar, the nuclear chromatin was somewhat more hyperchromatic than that seen in tanned control specimens (Fig 2).

In the acutely irradiated skin there were significantly fewer PMN in the tanned sites than in the untanned sites ($p = 0.001$). In addition, there was a significant correlation between the dose of acute UVA irradiation and the number of PMN ($p = 0.002$) (Fig 3). In contrast to PMN, there were far more MNC in tanned skin than in untanned skin. This difference was significant when tanned and untanned irradiated specimens were compared ($p = 0.006$), but there was no significant association between the dose of acute UVA irradiation and the number of MNC ($p = 0.10$). A similar difference in the MNC was seen in the tanned and untanned control

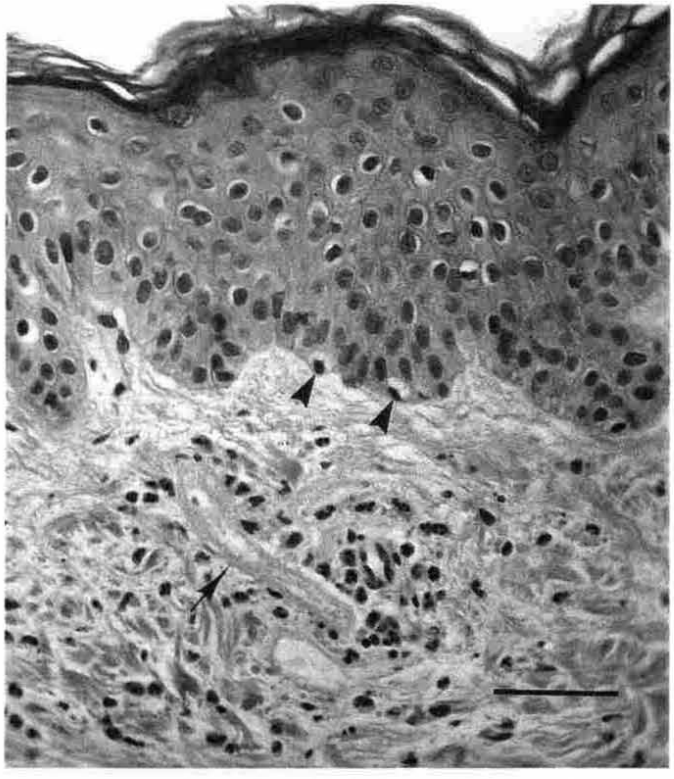

Figure 1. Untanned skin after 4 MED of acute UVA-irradiation. In the dermis there is a remnant of a necrotic blood vessel wall devoid of endothelial cells *(arrow)* adjacent to a blood vessel with prominent endothelial cells. PMN surround the blood vessels. In the epidermis there is scant intercellular edema, and the melanocytes have hyperchromatic round to oval nuclei *(arrowheads)*. (H&E stain: ×313; *bar:* 50 μm).

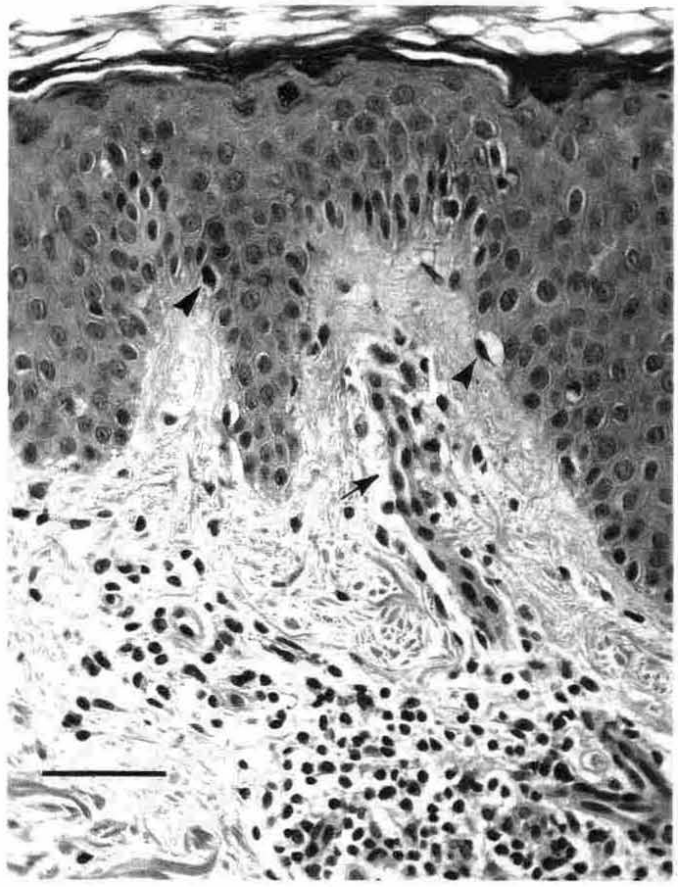

Figure 2. Tanned skin after 4 MED of acute UVA-irradiation. In the dermis there is a MNC infiltrate. The blood vessel wall is thicker than normal and has prominent endothelial cells *(arrow)*. In the epidermis there is scant intercellular edema, and the melanocytes have enlarged round to oval nuclei *(arrowheads)*. (H&E stain: ×313; *bar:* 50 μm).

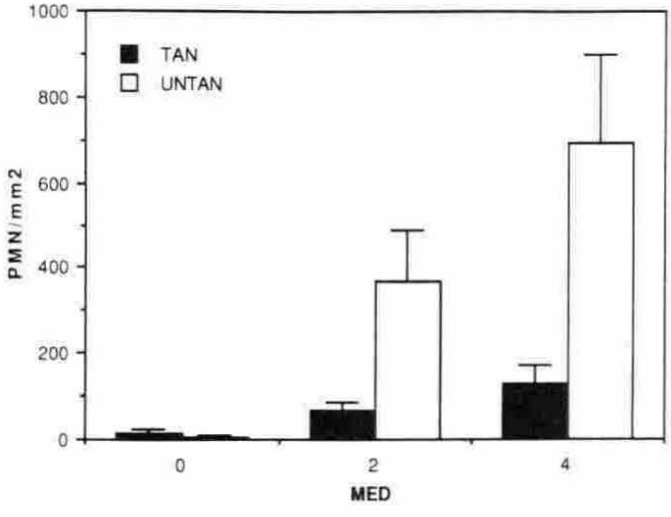

Figure 3. PMNs/mm² ± SEM in tanned and untanned skin after 0, 2, and 4 MED of acute UVA-irradiation. After acute UVA-irradiation there were significantly fewer PMN in the tanned than in the untanned skin ($p = 0.001$), and there was a significant correlation between the dose of acute UVA irradiation and the number of PMN ($p = 0.002$).

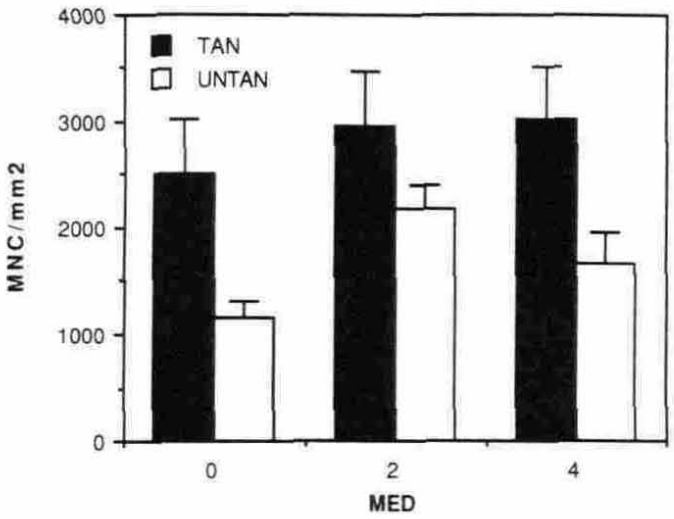

Figure 4. MNCs/mm^2 ± SEM in tanned and untanned skin after 0, 2, and 4 MED of acute UVA-irradiation. There were more MNC in tanned than in untanned skin. This difference was statistically significant when the tanned and untanned irradiated specimens were compared ($p = 0.006$), but was not significant in the control specimens ($p = 0.08$).

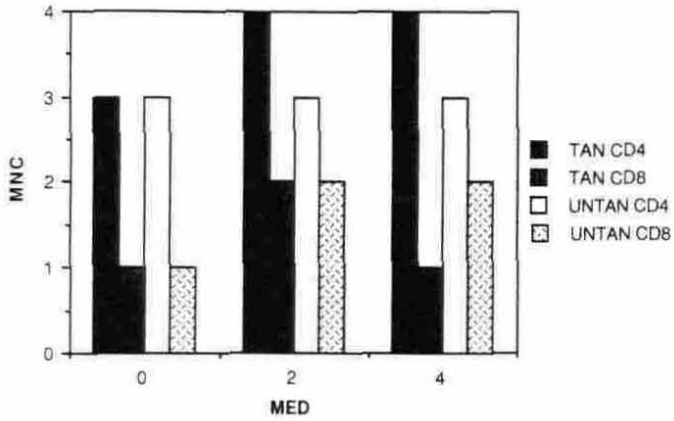

Figure 5. Semi-quantitative analysis of immunoperoxidase stained dermal MNC after 0, 2, and 4 MED of acute UVA-irradiation. In each case the number of CD4 positive cells exceeded the number of CD8 positive cells.

specimens. However, in this small sample, it was not statistically significant ($p = 0.08$) (Fig 4). The effects of tanning on PMN and MNC counts in subjects with types I and II skin were similar to those seen in subjects with types III and IV skin in this small sample. Although the mean difference of MNC between tanned and untanned skin was greater in the four subjects with types III and IV skin (1635 ± 518; mean ± SEM) than in the three subjects with types I and II skin (526 ± 643), the two mean differences were not significantly different from each other ($p = 0.2$) because of the large variation in the MNC counts among individuals within each group.

In the immunoperoxidase stained tissue sections, many more intraepidermal Langerhans cells stained with CD1a (OKT6) than with anti-HLA-DR antibodies (Table II). In both cases there were fewer stained cells in the tanned control than in untanned control skin, although these differences were not significant ($p = 0.10$ and 0.5, respectively). In addition, the number of cells in tanned sites was similar to the number in untanned sites after 2 and 4 MED of acute UVA-irradiation ($p = 0.6$ for both CD1a and anti-HLA-DR). Increasing doses of acute UVA-irradiation were associated with decreasing counts of CD1a ($p = 0.001$) but not anti-HLA-DR stained cells ($p = 0.2$). In the dermis, the majority of the MNC were CD3 positive T cells. Most of these were CD4 positive cells, and a smaller number were CD8 positive cells. Although the absolute number of cells differed in the various specimens, the ratio of CD4/CD8 positive cells was similar in tanned and untanned skin regardless of the amount of acute UVA irradiation (Fig 5). Occasional CD8 positive cells were seen in the epidermis in the untanned acute UVA irradiated specimens. There were also anti-HLA-DR, CD11, and anti-HLA-DQ positive mononuclear cells in the dermis along with perivascular CD1a positive dendritic cells. These were greater in the tanned than in the untanned skin, regardless of the amount of acute UVA-irradiation.

Table II. Epidermal Langerhans Cells/Linear mm of Epidermis in Immunoperoxidase Stained Tissue Sections (Mean ± SEM)

	CD1a (OKT6)		
	Control	2 MED	4 MED
Tanned	21.85 ± 2.62	22.64 ± 3.01	17.18 ± 3.90
Untanned	30.56 ± 3.38	23.60 ± 3.63	17.58 ± 2.42
		anti-HLA-DR	
Tanned	8.89 ± 2.82	13.74 ± 2.73	10.49 ± 3.00
Untanned	11.00 ± 3.49	13.32 ± 2.08	12.71 ± 2.51

DISCUSSION

In this study we evaluated the effect of a UVA tan on acute dermal injury after further UVA irradiation in order to determine whether or not UVA-induced pigmentation had a physiologic role in protection of dermal structures, particularly blood vessels, and inhibition of acute inflammation. By histologic criteria, we observed that a UVA tan provided significant protection against acute UVA-irradiation. Not only was the acute inflammatory cell infiltrate significantly less, but there was also no vascular necrosis and much less endothelial cell enlargement in the tanned than in the untanned skin after acute UVA-irradiation.

Endothelial cell enlargement and necrosis have previously been observed after acute UVA irradiation, and it has been speculated that the endothelial cell is the primary target for UVA induced injury [5–8]. After UVC and UVB irradiation the inflammatory cell infiltrates are similar, but endothelial cell injury has not been seen [5,9]. Preliminary studies, using an antibody that reacts with activated endothelial cells (monoclonal antibody H4/18), have shown the presence of H4/18 binding antigen in acutely irradiated tanned and untanned specimens as well as in control tanned skin, but there was no endothelial cell staining in unirradiated control skin (unpublished observation in collaboration with R. Cotran) [18]. Although it has not been shown whether UVA increases interleukin-1 (IL-1) or tumor necrosis factor (TNF), two cytokines that induce this antigen, it has been shown that UVB radiation results in increased IL-1 production by keratinocytes in vitro and increased serum or plasma levels in mice, rabbits, and humans in vivo [19–25]. UVA irradiation does result in increases in arachidonic acid, prostaglandins, and histamine in human skin in vivo, and UV-irradiation of cultured keratinocytes results in the release of a leukotriene-B_4-like material [8,26,27]. However, the relationship between these molecules and activation of endothelial cells is not known.

The long-term effects of UVA-radiation have been studied in mice, and they include elastosis and increases in glycosaminoglycans [4,28]. Our finding of a MNC infiltrate 7 d after the last tanning exposure suggests that the chronic photodamage induced by UVA irradiation may in part be mediated by the persistent MNC infiltrate. This may result from the fact that lymphocytes and other cells may release cytokines that alter collagen homeostasis. For example, γ-interferon, which is produced by activated T lymphocytes, inhibits collagen production, while IL-1, which is produced by a number of different cells, increases collagen production [29,30]. It is then possible that UVA-induced photodamage may, in part, result

from a net decrease in collagen and other dermal components because of the cytokines released by the MNC.

In addition, in this study, as in others, UVA-irradiation diminished surface markers on the intraepidermal Langerhans cells [8,31]. However, the functional consequence is not clear. Prior irradiation of skin with UVB-radiation has been shown to result in a decreased ability to be sensitized to chemical haptens, whereas exposure to doses of UVA radiation that alter Langerhans cell morphology has resulted in an enhanced contact hypersensitivity response [32,33]. Furthermore, tanning and acute UVA irradiation had more of an effect on the CD1a staining than anti-HLA-DR staining of Langerhans cells. Although it is unclear why this would occur, CD1a is superior to HLA-DR as a marker for Langerhans cells because many of these cells are CD1a but not HLA-DR positive [34]. In view of this, the changes in CD1a staining may more accurately reflect the changes in Langerhans cells after UVA-irradiation.

These findings demonstrate that a UVA-induced tan is photoprotective, limits the acute response to further UVA-irradiation, and that repeated exposure to UVA results in a persistent MNC infiltrate and vessel wall thickening. These findings suggest that while a UVA-induced tan protects against the acute UVA effects in the dermis, repeated exposure to UVA results in a persistent MNC infiltrate. While direct correlation of these findings with the clinically deleterious effects of chronic UVA exposure is not possible at this time, the inflammation that results from both acute and chronic exposure to UVA supports the notion that it is desirable to limit exposure to UVA radiation.

In the future, the histologic techniques used to quantify the inflammatory infiltrates may be used as a model to evaluate the efficacy of UVA sunscreens, while other techniques will be needed to determine the pathogenesis of endothelial cell injury, the recruitment of inflammatory cells, and the duration and long-term effects of the MNC infiltrate.

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ERRATUM

In the article by Peter M. Ross and D. Martin Carter entitled "Actinic DNA Damage and the Pathogenesis of Cutaneous Malignant Melanoma" (JID 92:293S–296S, 1989), one publication was omitted from the list of references at the end of the paper. Reference 57 should be: Ross PM: Apparent absence of a benign precursor lesion: Implications for the pathogenesis of malignant melanoma. J Am Acad Dermatol (in press). The original Refs 57 and 58, in the reference list, should be renumbered as 58 and 59, respectively.